

### ABSTRACT OF THE DISCLOSURE

1           Methods for the preparation of a lipid-nucleic acid composition are provided.  
2    According to the methods, a mixture of lipids containing a protonatable or deprotonatable lipid,  
3    for example an amino lipid and a lipid such as a PEG- or Polyamide oligomer-modified lipid is  
4    combined with a buffered aqueous solution of a charged therapeutic agent, for example  
5    polyanionic nucleic acids, to produce particles in which the therapeutic agent is encapsulated in a  
6    lipid vesicle. Surface charges on the lipid particles are at least partially neutralized to provide  
7    surface-neutralized lipid-encapsulated compositions of the therapeutic agents. The method  
8    permits the preparation of compositions with high ratios of therapeutic agent to lipid and with  
9    encapsulation efficiencies in excess of 50%.